CHRONIC FAMILY JAUNDICE.

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IN recent years considerable attention has been attracted to a remarkable disease, characterized by chronic non-obstructive jaundice with enlargement of the spleen, and usually occurring in hereditary form, or in several members of one family. In spite of a goodly number of reports from Germany, England, and especially from France, the condition has attracted little notice in this country, and no articles on the subject have appeared. That chronic family jaundice is far from rare is shown by the fact that we have been able, within a short space of time, to investigate four such families.

The first accurate account of the disease was given by Minkowski in 1900, though Murchison, fifteen years before, described a family showing hereditary jaundice, and Hayem, in 1898, reported, under the title, chronic infectious splenomegalic icterus, cases which have since been shown to belong to the condition in question. The family reported by Wilson in 1890 also belongs here, but was not thoroughly investigated.

The important features are as follows: Jaundice appears in several members of a family, frequently in two, three, or even four generations. It dates either from birth, or is first noticed during adolescence, and persists throughout life, yet in spite of the long duration, the patient experiences little inconvenience from his complaint, and may attain an advanced age. The growth of these children is not interfered with. The icterus is usually not intense, there are no signs of obstruction of the bile ducts, and symptoms of cholemia, such as itching, slow pulse, xanthomas, and multiple hemorrhages, are lacking. The stools are highly colored, and the urine contains urobilin, but no bile. Enlargement of the spleen, which may reach huge proportions, is almost a constant feature, while the liver is usually not at all, or only slightly enlarged. As a rule, there is a moderate grade of anemia. "Bilious attacks" are extremely common, especially in youth; after an indiscretion in diet, a period of constipation, or without obvious cause, the patient feels tired and depressed, the jaundice deepens, and there is repeated vomiting of bile. Headache, diarrhœa, and slight fever are occasionally noted. After a day or two the attack passes off, to recur usually several times a year. Attacks of abdominal pain, located in the epigastrium or right hypochondrium, are met with in a large proportion of cases, and are due, as will be shown later, to a complication with gallstones. The enlarged spleen often causes a feeling of weight and pressure in the left side of the abdomen, and pain in this region, sometimes accompanied by a friction rub, is a not infrequent occurrence, owing to a complication with perisplenitis. A history of nose-bleed, particularly during adolescence, is almost always to be obtained, but hemorrhages from other organs, and especially from the stomach and intestines, are not met with, an important distinction from splenic anemia and cirrhosis. Apart from the attacks mentioned above, the subjects, as Chauffard aptly remarks, are rather jaundiced than sick. However, there is often a feeling of lassitude and a tendency to somnolence.

TYPES OF THE DISEASE. Besides the usual form in which the disease is hereditary, and others in which it is familial, in the sense that several brothers or sisters are affected while the parents are not, there is a "congenital" form, in which the disease appears in only one of a family, and dates from birth. This latter type does not differ in any way from the common form, except in the absence of heredity. Another type is the so-called "acquired" form, in which the disease appears first in childhood or adolescence, rarely later. Many of the cases are undoubtedly identical with the hereditary form, in which it not seldom happens that the jaundice is first noticed in youth (such as our Cases V, VII, X, and XII). There is always a possibility that slight jaundice was present earlier, but escaped detection. In other cases the acquired form shows some divergences from the hereditary, especially in the severity of the anemia, which may even simulate pernicious anemia. In the cases of Stejskal and Chauffard the red count fell below one million, but pernicious anemia could be excluded by the morphology of the red cells, and the presence of *increased* fragility of the red cells; in pernicious anemia the fragility is *decreased*. The postmortem appearances in acquired cases have been identical with those in the hereditary type, and for the present it is permissible to conclude that the acquired and the hereditary form are only different manifestations of the same disease, just as we see in other diseases which are usually hereditary (such as progressive muscular dystrophy) cases which are apparently "acquired."

THE JAUNDICE. In well-marked instances the conjunctivæ are a lemon-yellow color, and the skin of the body is distinctly yellow, while the face is of a peculiar buff color which is quite characteristic. The greenish or blackish tint seen in long-standing total obstruction of the bile ducts is never present. In light cases the yellowness is apparent only on careful scrutiny. The jaundice varies in intensity from time to time, being more marked in some patients during the cold weather, in others in the summer. Fatigue and sometimes emotion may cause an increase in the jaundice, and at such times the patients, as a rule, complain of lassitude and depression. Intercurrent diseases, and even taking cold, may cause an increase. Once present, the jaundice persists throughout life. An apparent exception to this rule is seen in Plehn's first case, who was very yellow as a child, but never later, and at sixty-one showed only anemia and enlarged spleen. (No examination of the serum for bile was made.) Poynton and a few others have observed recurrent attacks of jaundice with only anemia and splenic tumor in the intervals. As the blood serum was not examined for bile, it may be questioned if a slight degree of icterus in the interval did not escape detection.

THE URINE. The urine is almost always high colored. Urobilin is present in the great majority of cases, being missed chiefly in those of slight intensity. Urobilinogen is also almost always to be found. On the other hand, bile is absent from the urine almost invariably, and when found is usually in small quantities and as a transitory phenomenon. The twenty-four hour amount is normal. There is frequently a deposit of urates, and sometimes of uric acid; in one of our cases (VII) showing such a deposit, the total endogenous uric acid was increased. We have found the normal urinary pigment (urochrome) constantly increased, and this accounts in large measure for the reddish-yellow color of the urine, which is present even in cases showing no urobilin. Hematoporphyrin is always absent.

THE STOOLS. In all reported cases the feces have been well-colored, and in those that we have examined they have seemed to contain an excess of pigment, judging from the intense orange or brown color. A marked reaction for urobilin is obtained with corrosive sublimate, and an intense fluorescence with Schlesinger's test for urobilin. These facts, together with the urobilinuria, point to an increased secretion of bile into the intestine, and Möller has, in fact, shown by quantitative methods that the total urobilin excretion in the urine and feces is considerably increased (400 milligrams in twenty-four hours). Unaltered bilirubin is absent or present only in traces. The guaiac test for occult blood has been uniformly negative in our cases. The feces show no excess of fat, starch, or muscle fibers, and quantitative analysis in one of our cases (VII) showed normal proportions of neutral fat, fatty acids, and soaps, as was to be expected. Constipation is often present, but not with regularity, several of our patients passing two or three soft stools daily.

THE BLOOD.—The serum always shows the presence of bile pigment, but not of urobilin. The important feature, which gives our chief clue to the nature of the disease, is the decreased resistance of the red cells to hemolyzing agents; or as it is sometimes called, the increased fragility. This was first discovered by Chauffard, and has been present, with very few exceptions, in all the cases in which it was looked for. The usual method of testing for it is by mixing the red blood cells, preferably after separation from the plasma, with hypotonic solutions of sodium chloride of varying strengths, and noting the point at which hemolysis takes place. With normal blood hemolysis begins in salt solutions of 0.44 per cent., and is complete at 0.36 per cent. In the case of chronic family jaundice, however, hemolysis begins at 0.6 per cent., or even 0.7, and may be complete at 0.5 per cent. This marked decrease of resistance is all the more important, because in chronic obstructive jaundice the resistance is normal or *increased*. As Chauffard has shown, this lessened resistance is evident also when tested with other hemolytic agents, such as eel serum and antihuman serum. Hemolysins, however, have never been found in the blood serum, though often looked for, and hemagglutinins have been found in only one case (Hawkins and Dudgeon). Hemoglobin has been found in the blood serum in only two cases, those of Bettmann and Chauffard. Bettmann's patient frequently had attacks of prostration with increased jaundice after exposure to cold. The author was able to induce such an attack artificially by means of immersion of the hands in ice water, and then found large amounts of hemoglobin in the serum and later in the urine. In Chauffard's case oxyhemoglobin was found in the serum during a routine examination. Such phenomena are probably quite exceptional in chronic family jaundice, but are interesting in connection with the hemolytic theory of its causation. They do not prove any close relationship to paroxysmal hemoglobinemia.

A moderate anemia is the rule, with red counts usually in the neighborhood of three or four millions. The lowest count in the hereditary type was 1,500,000 (Benjamin and Sluka), while occasionally normal figures are reported, and in two cases abnormally high counts (Mosse, 7,800,000; Guinon, Rist, and Simon, 7,200,000). In Mosse's case, however, the jaundice was acquired at the late age of fifty-four years, so that it may be doubted if it belongs with the disease under consideration. It differed from the ordinary type of polycythemia by the lack of cyanosis and the presence of acholuric jaundice. In the other case, also acquired, the polyglobulia was transient and accompanied by cyanosis.

The color index is usually normal, the hemoglobin being reduced in proportion to the red count. The red cells are usually well colored. There is well-marked anisocytosis, with microcytes predominating. When measurements have been made, the average diameter has been found decreased. Thus out of six cases in which we measured the cells, the diameter was decreased in five, averaging 6.5 microns, and normal in one. Usually there is little poikilocytosis, and some polychromatophilia, but punctate basophilia is rare. Reticulation of the red cells, as brought out by the so-called "vital" method of staining, is apparently a constant feature, and is considered by Chauffard an important diagnostic sign if present in a considerable proportion of the cells. Nucleated red cells in small numbers are often found, usually in the form of normoblasts. In two of our cases there were isolated megaloblasts, of the intermediate variety; that is, with small deeply staining nucleus. The blood plates are present in normal numbers. The leukocyte count is usually within normal limits, sometimes subnormal and exceptionally increased. The differential count shows nothing striking except for a tendency toward high values for the polynuclear neutrophiles, and the occasional presence of rare myelocytes. The blood picture differs from that of the ordinary secondary anemia in the normal color index and the more frequent appearance of nucleated red cells.

THE LIVER. The liver is usually of normal size, or slightly enlarged, seldom reaching more than one finger's breadth below the edge of the ribs. Some have noted that during exacerbations of the jaundice the liver swells, to return to its former size after the attack is over. Signs of cirrhosis, such as hardness, irregularity, or marked alteration in size of the liver, ascites, and evidences of collateral circulation, are conspicuous by their absence. The bile, in the only case in which it was examined (our Case VII) was of a deep golden-red color, evidently very rich in pigment, and was sterile.

Attacks of abdominal pain resembling biliary colic have been observed in a large proportion of cases, and have been often supposed to be caused, in some mysterious way, by the disease itself. In two of our cases (VII and IX), however, gallstones were removed at operation, after which the attacks ceased, and in both our autopsies (Cases I and II) stones were found in the gall-bladder, so that we have no hesitation in declaring that these attacks are due to gallstones. A striking feature is the frequent onset of the colic at the time of puberty, a period at which ordinary cholelithiasis is seldom met with. The pain is sometimes located in the region of the spleen, and is then due to perisplenitis, for friction rubs have been heard over the spleen and inflammatory changes in the capsule have been found at autopsy. The pain of perisplenitis, however, is different from that of gallstone colic, being usually dull and not paroxysmal.

THE SPLEEN. The presence of splenic tumor forms one of the most striking features of the disease, and has often led to the false diagnosis of splenic anemia. It is practically always palpable, in well-marked cases extending down to the level of the navel, and occasionally reaching the proportions of a leukemic spleen, as in our Case VIII, in which it filled the entire left side of the abdomen. In a few instances no enlargement of the spleen was found, though all the other characteristics of the disease were present. In Case III of Benjamin and Sluka, the grandfather showed no splenic enlargement, while the son and granddaughter both were typical cases with very large spleens. There is therefore no reason to make a separate category out of the cases without splenic tumor.

THE HEART. This organ shows no abnormalities, except for a soft systolic murmur in the pulmonary area, due to the anemia.

THE METABOLISM. Tests for alimentary glycosuria and levulosuria have been almost constantly negative. In our Case VII, however, a moderate excretion of sugar was noted after the ingestion of glucose, and also after levulose; it was not determined in the latter instance whether the sugar excreted was dextrose or levulose. In this same case normal values were found by one of us (Tileston) for creatin, creatinin, urea, and ammonia; the patient was on a creatin-free diet.

COMPLICATIONS. True gout has been associated in a few instances, notably in the family described by Murchison, and in our Cases I, IV, and XI. Articular pains, usually without joint changes, are somewhat frequently reported, and great importance has been attached to them by French observers, who make them a part of the "hepatic diathesis" ("hépatisme" of Glénard). They are not a constant feature by any means, and in our opinion have no important bearing on the disease. The various forms of chronic arthritis and arthralgia, particularly in elderly persons, are so common that it is easy to get a history of them in some members of almost any family. Urticaria is not uncommon. The complication with gallstones has already been discussed.

PATHOLOGY. Only eight autopsies have been performed, in the cases of Minkowski, Vaquez, Gandy and Brulé, Oettinger, Strauss, Wilson, and our Cases I and II. The cases of Strauss and Oettinger were acquired, the others hereditary; the pathological picture was the same in both types. The liver has been found normal in size, with no obstruction of the bile ducts, and no cirrhotic changes. Evidences of cholangitis have been lacking, except in our Case II, in which there were dilatation and thickening of the common duct, evidently secondary to gallstone disease. In all cases there was a considerable deposit of brownish pigment within the liver cells; this pigment contained iron in Vaquez's case, in Minkowski's it did not. In five of the eight cases stones were found in the gall-bladder. The spleen is greatly enlarged (up to 1000 grams), and usually shows signs of old perisplenitis; the increase in size is due mainly to increase of the pulp, the trabeculæ being, as a rule, not much enlarged, and the follicles normal, or, as in the case of Wilson, sclerosed. Microscopically the striking feature is the marked engorgement with blood; this in one-half of the cases was most marked in the pulp, the sinuses containing little blood. There is more or less pigment in the organ, usually within endothelial cells. The amyloidosis found in our Case I was probably to be attributed not to the disease itself, but to the complication with gout. The kidneys in Minkowski's case contained a very large amount of iron, both as pigment and in combination with an albuminous body; in the other cases there was little pigment in the kidneys. The bone marrow is found in a state of intense reaction; there is red marrow in the femur and numerous normoblasts, myelocytes, and polynuclear cells are seen.

HEREDITY. The disease is in most instances an exquisitely hereditary affection, frequently involving three or even four generations. It is transmitted equally by the male and by the female, and Wilson's statement that it is usually transmitted from father to daughter, and from mother to son, does not hold good for most instances. There are families in the literature in which only females are affected, and others in which the males are the ones to show jaundice. In a large series, however, the sexes are involved about equally (55 males and 45 females in 100 cases). There seems to be no racial predisposition. ~~Some of the children almost always escape, and~~ the offspring of those who do are always free from the disease.

ETIOLOGY AND PATHOGENESIS. Various theories have been propounded to account for this strange disease. Two may be dismissed from the start—the second theory of Pick, of a congenital communication between the bile passages and the lymphatics, and Hayem's latest view, that it is due to syphilis. The former is disproved by the autopsies, the latter by the entire lack of proof of the existence of syphilis in these families, and by negative Wassermann reactions in the four cases of Weber and Dorner.

The icterus present is certainly of the type known as polycholic, or, perhaps more correctly, pleiochromatic. That is to say, it is due to an excess of biliary pigment, not to obstruction of the bile ducts. This is shown by the fact that the stools are well colored, and the total urobilin output increased, as shown by Möller, and by the absence of any obstruction of the bile ducts, small or large. The presence of *temporary* obstruction of the bile ducts must be admitted for a few cases, in which with increased jaundice and usually colicky pains in the abdomen the stools became clay-colored, but these exceptions are readily explained by a complication with gallstones, which is common.

Let us next consider the first theory of Hayem, that the icterus and splenic enlargement are due to a chronic cholangitis. This view has very little in its favor, for it is difficult to conceive of a chronic infection of the bile-passages sufficient to produce jaundice dating from birth, and persisting through many years, and yet leaving no traces visible at the postmortem examination.

Minkowski believes that the disease is due to a congenital perverted function of the liver cells, by virtue of which the bile is secreted in part into the lymphatics instead of into the bile capillaries. Under normal circumstances the liver cells secrete sugar into the lymphatics and bloodvessels, and bile into the bile passages. It is easy to conceive that this selective action might be interfered with, so that part of the bile would go the wrong way. This hypothesis would account for the jaundice, but not for the excess of bile pigment, nor for the enlargement of the spleen. Moreover, the jaundice may be explained solely on the ground of pleiochromia, for it has been shown that an excess of bile pigment is accompanied by increased viscidity of the bile, which raises the pressure in the bile passages and thus produces in a sense a mechanical obstruction to the flow of bile, and consequently jaundice.

The discovery by Chauffard of the increased fragility of the red cells threw a new light on the disease, and apparently explained the various phenomena in a satisfactory way. The red cells, being unduly susceptible to the action of hemolyzing agents, are readily destroyed, and this leads to the anemia which is so constant a feature. The bone-marrow is stimulated by the deficiency in red cells to increased activity, shown in the circulating blood by the presence of nucleated red cells and at times an increased proportion of polynuclear leukocytes, and a few myelocytes. The increased destruction of red cells leads to an increase in the material (free hemoglobin) out of which bile pigment is made, and hence to pleiochromia and icterus. Such a "hemolytic icterus" can be produced experimentally, as Lesné and Ravaut and others have shown, by the injection of hemolytic agents, which is followed by jaundice, increase in size of the spleen, and, depending upon the size of the dose, by the appearance of urobilin, bile, or hemoglobin in the urine.

Since no hemolysins can be demonstrated in the blood, the increased destruction of red cells probably takes place not in the blood, but in the spleen, that "graveyard of the red corpuscles." This leads to increased work on the part of the spleen, and hence to the progressive enlargement of the organ.

This hemolytic theory offers the best explanation of the phenomena observed, and is the one generally accepted by recent writers. The ultimate cause of the increased fragility of the red cells remains to be discovered. Two hypotheses are possible: (1) That there is a congenital defect of metabolism leading to the production of toxic substances deleterious to the red cells; and (2) that there is a congenital defect in the blood-forming organs.

TERMINOLOGY. As often happens in diseases of obscure causation, a multitude of names has been proposed, depending on the theory of the writer with regard to etiology, and whether the hereditary, the familial, or the congenital aspect is emphasized. For example: Chronic infectious splenomegalic icterus, chronic acholuric hereditary jaundice, congenital hemolytic icterus, chronic family cholemia, etc. Until more is known about the pathogenesis, the term chronic family jaundice may be recommended on the ground of simplicity and clearness.

OTHER FAMILIAL DISEASES ASSOCIATED WITH JAUNDICE OR WITH SPLENIC TUMOR. There are a few other affections which may occur in several members of a family, and show more or less resemblance to chronic family jaundice.

1. *Congenital Obliteration of the Bile Ducts.* This process, due either to congenital malformation or to inflammatory changes, leads to intense obstructive jaundice, visible at birth. It is incompatible with the long continuance of life. In some cases, however, there is only stenosis of the common duct, and the patient may live many years, with jaundice and partial decolorization of the stools; the gall-bladder is greatly dilated, from which fact and the time of appearance of the icterus the diagnosis can be made.

2. *Fatal Icterus Neonatorum without Obstruction of the Bile Ducts.* Very rarely families are met with in which almost all of the children, and they are many, become deeply jaundiced a few days after birth, and usually die within a period of days or weeks, often with convulsions. Bile is found in the urine, but the stools are well colored. Those infants which do not die early recover from the jaundice completely, but are very anemic for a while afterward. At autopsy nothing has been found to account for the jaundice; in particular there has been no obstruction of the bile passages, and no evidence of septic processes or syphilis. A curious feature is the "Kernicterus" of Schmorl; the ganglia at the base of the brain are an intense yellow, while the rest of the brain is only slightly icteric; the yellow areas show necrosis of the nerve cells. This type of icterus is peculiar to jaundice of the newborn, and has been reported chiefly in connection with the family type.

3. *Juvenile Family Cirrhosis.* Cirrhosis occurring in two or more children of a family has been described by a number of writers. A few of these cases may be attributed to hereditary syphilis, some others to the use of alcohol or other irritating substances; thus, the two children reported by Jollye (*Brit. Med. Jour.*, 1892, i, 858) both drank vinegar in large quantities. For the majority, no cause could be made out. The course resembles that of Hanot's cirrhosis, ending fatally before the twentieth year. The growth is usually stunted.

4. *Familial Splenomegaly of the Gaucher Type.* This truly remarkable disease, first described by Gaucher in 1882, is characterized by enormous enlargement of the spleen (up to 7000 grams) lasting over many years, usually occurring in several members of a family, and affecting females almost exclusively. The liver is always considerably enlarged. Anemia is seen, and brown pigmentation of the skin, but jaundice is seldom, and ascites never, present. The histological appearances are pathognomonic. The spleen, bone-marrow, lymph nodes, and in the liver the ramifications of Glisson's capsule show large numbers of peculiar cells, with small nuclei and much protoplasm. Marchand has recently shown that the large size of the cells is due to a deposit of a homogeneous material like hyaline, the nature of which could not be determined.

DIAGNOSIS. Chronic family jaundice is easily recognized, if the disease is only borne in mind. The great enlargement of the spleen with anemia has led to the false diagnosis of splenic anemia, or Banti's disease; the latter diagnosis was made in our Case XII by a well known European clinician. The occurrence of jaundice in other members of the family, the chronicity, the early onset, the presence of bile in the feces and its absence from the urine, the changes in the blood, and the enlargement of the spleen without enlargement of the liver or indications of cirrhosis, are the important diagnostic points. From juvenile cirrhosis it is distinguished by the absence of marked enlargement of the liver, the absence of stunting of the growth, the absence of bile in the urine, and the course of the disease. Splenomegaly of the Gaucher type may be excluded by the presence of jaundice, the absence of marked enlargement of the liver, and by the fact that Gaucher's disease is familial but not hereditary. The acquired form of chronic family jaundice is distinguished from pernicious anemia by the increased fragility of the red cells in the former, and by the morphology of the blood. The frequent complication with gallstones has led to the diagnosis of jaundice due to obstruction of the common duct by calculi. This error can be avoided by attention to the above mentioned points.

PROGNOSIS. The prognosis is good so far as life is concerned, absolutely bad with regard to recovery. The prospects are good that some of the offspring will be free from jaundice.

TREATMENT. No measures have any effect on the jaundice or splenic tumor, not even the Röntgen rays. The anemia is said to have been benefited in certain cases by the use of iron, while arsenic is useless. The most that can be done is to regulate the life of the patient in such a way as to avoid the factors that tend to increase the symptoms (fatigue, excitement, indiscretions of diet, etc.). It should be realized that attacks of abdominal pain are not due to the disease *per se*, but to a complication with gallstones, and the patient should be given the benefit of modern surgical treatment, which has been neglected heretofore in all cases except VII and IX of our series.

In concluding we present the reports of thirteen cases, occurring in four families. The first of these families was investigated by Dr. Griffin, the others by Dr. Tileston. To economize space, many details have been omitted. In the urine sugar was always absent, and also acetone and diacetic acid. Urochrome was increased in all but Case XI. Albumin was absent unless otherwise specified.

Family I. Jaundice in at least seven members in three generations. Autopsies in two cases.

This family is remarkable for the frequency with which the condition has been associated with gallstone colic (five out of seven cases), and with gout.

CASE I.—O. S., male. Concerning his parents little is known, but a cousin of his father was jaundiced for many years, and suffered from severe attacks of colic. O. S. was the third of thirteen children, ten of whom lived to grow up. One brother (H. S. S., Case II) had the same disease, and a sister was jaundiced all her life, and suffered from gallstones. O. S. was jaundiced from birth, suffered frequently from attacks of biliary colic, and died at the age of seventy-four. Of his four children, the first two were jaundiced (Cases III and IV).

Autopsy, May 22, 1900, Harvard Medical School, U—00—15, performed by Dr. F. T. Fulton, to whom we are indebted for the notes. There are extensive gouty lesions, consisting of marked deformity of the fingers and toes, with many sodium urate deposits (tophi) in the vicinity of these joints, and in the kidneys. The *spleen* is much enlarged, and firm; the capsule is thickened, with fibrous tags adherent. On section the trabeculæ are prominent, the follicles not easily made out, the pulp not increased. The *liver* is not enlarged, of normal consistency, and on section brownish red. The *gall-bladder* is considerably distended with dark green bile, and contains 13 pigmented calculi. The bile passages are normal. There are old adhesions between the gall-bladder and the foramen of Winslow. The *kidneys* are small, granular, the capsule adherent, the cortex thinned, the pelvis dilated. The left kidney contains some cysts and a small abscess. There are also hypertrophy of the prostate, arteriosclerosis, hypertrophy and dilatation of the heart, and acute pericarditis.

Microscopic Examination of the Spleen. In frozen sections treated with iodine the walls of many of the smaller vessels, and certain areas closely surrounding these vessels, are stained a mahogany-brown. Sections stained in the usual way show considerable congestion, and a general increase of the interstitial connective tissue. The pulp consists of lymphocytes and red blood cells. Throughout the pulp there is considerable golden-yellow pigment, chiefly within endothelial cells. The lymphoid cells of the follicles have almost entirely disappeared, their place being taken by small pinkish masses of hyaline material (amyloid); the walls of the smaller arteries are distinctly thickened and hyaline. "The pigment is probably derived from red blood corpuscles" (F. B. Mallory).

Microscopic Examination of the Liver. Frozen sections show no excess of fat. With iodine the walls of the smaller interlobular vessels, and small scattered areas among the liver cells give the reaction for amyloid. There is no increase of the interstitial connective tissue, and the bile capillaries are normal. There is considerable brownish pigment within the liver cells. In minute areas the liver cells are entirely gone, their place being occupied by masses of amyloid.

Microscopic Examination of the Kidneys. There is a marked chronic diffuse nephritis with extensive amyloid infiltration; also an acute inflammatory process in the collecting tubules. (Ascending infection). No pigment is seen.

Case II.—H. S. S., brother of O. S. (Case I). When first seen in July, 1903, for bronchitis, he was seventy years old. He said he had been slightly jaundiced all his life. Examination showed icterus of the skin and eyes, great enlargement of the spleen, which reached from the sixth space to the level of the navel, and a liver of normal size; myocardial insufficiency. January 4, 1904, he was seen again for a severe attack of pain in the right hypochondrium, with tenderness over the region of the gall-bladder, fever, and leukocytosis. The stools were dark colored and the urine free from bile, while the skin was more yellow than usual. The spleen had not changed in size. This attack of cholecystitis lasted, with intermissions, for six weeks. On February 8, 1907, he was seized with his final illness, a lobar pneumonia, to which he succumbed on the 19th. An autopsy was performed by Dr. L. J. Rhea, of the Department of Pathology, of the Harvard Medical School, who has very kindly placed the notes at our disposal.

Autopsy U—07—18. February 19, 1907, by Dr. L. J. Rhea. The scleræ and skin have a distinctly yellowish tint. *The spleen* is markedly increased in size, and is united by firm adhesions to the diaphragm. The consistency is somewhat increased. On section it is deep red in color; the follicles are easily made out, the trabeculæ are just visible. *The liver* is apparently not larger than normal, the cut surface dark brownish red. The bile ducts stand out rather prominently. The common duct is patent. There are dense adhesions between the gall-bladder and the duodenum. The walls of the gall-bladder are thickened, and its cavity filled by a large black calculus. No stones are in the common duct or in the bile ducts within the liver. The common duct is quite markedly dilated and its walls thickened. There are also resolving pneumonia, chronic myocarditis, generalized arteriosclerosis, mural thrombi in the heart, chronic adhesive pleurisy, chronic nephritis and a persistent thymus gland.

Microscopic Examination. Spleen: The capsule is considerably thickened by dense fibrous tissue. The organ contains a large amount of blood which is in the pulp, not in the sinuses. The latter are narrow and appear compressed. Scattered throughout the organ are a few endothelial cells containing brownish pigment; some of the endothelial cells lining the sinuses, and in the capsule, contain similar pigment. *Liver:* There is a *slight* increase in the connective tissue between the columns of liver cells. The latter show quite a large amount of pigment in the form of fine scattered granules. The bile ducts are everywhere patent and their walls are not thickened. The sinusoids are moderately distended with blood and show some increase in lymphocytes, and a good many endothelial cells, which are phagocytic to red blood corpuscles, and polynuclear leukocytes. *Kidney:* There is a sclerotic process involving small localized areas.

Scattered tubules show numerous small brownish pigment granules within the epithelial cells.

Case III.—H. B. S., aged fifty-five years, son of O. S. (Case I). First child. He has been jaundiced since birth, but the color now is less intense than formerly, having faded in the last twenty years. "Slow fever" (probably typhoid) in youth. Until he was forty he was subject to frequent attacks of gallstone colic so severe that operation was asked for, but refused by the surgeon on account of the long-continued jaundice. He has bled profusely from the left nostril at times, but does not bleed much after cuts. Feces and urine have been always dark. He has been troubled for a long time by rheumatic pains, with some deformity of the smaller joints.

Physical Examination, February, 1910. The skin has a yellowish tinge, evident on close inspection; the conjunctivæ are more deeply yellow. The liver is slightly enlarged to percussion and the edge is palpable on deep inspiration about two fingers' breadths below the costal margin. The spleen is enlarged to percussion and palpable at the edge of the ribs with deep breathing. *Urine:* High-colored, with deposit of urates. Bile pigment and urobilin both absent. *Blood:* Leukocytes, 13,200; moderate poikilocytosis, slight polychromatophilia. Differential count: Polynuclear neutrophiles, 80 per cent.; small lymphocytes, 13 per cent.; large lymphocytes, 7 per cent.; eosinophiles, 0 per cent. No nucleated red cells. The *serum* contains bile pigment (iodine test.)

R. S., the son of this patient, aged twenty-six years, has never been deeply jaundiced, though the color of his skin has always been dark. He has been subject "all his life" to attacks of vomiting, with pain in the epigastrium, sometimes in the right hypochondrium. Appendectomy done three years ago has had no influence on the attacks. Stools always colored so far as known. Examination shows nothing abnormal except a slight icteroid tint of skin and conjunctivæ. No enlargement of the liver or spleen could be made out. This case is probably one of chronic family jaundice, but in the absence of splenic enlargement and definite jaundice the diagnosis is not certain.

Case IV.—O. A. S., aged fifty-one years. Brother of H. B. S. (Case III) and son of O. S. (Case I). Second child. He probably has been slightly jaundiced all his life, though he did not notice it until adolescence. The yellow color has never been marked, but is slightly greater during digestive upsets. Stools always brown. He has a tendency to indigestion, but there are no attacks of vomiting or abdominal pain. "Slow fever" as a boy, pneumonia at twenty-nine. During the past twenty-five years several typical attacks of pain in the great toe (gout).

Physical Examination, February 1910. Well developed and nourished. Skin sallow, conjunctivæ slightly yellow. *Spleen:*

Enlarged, from the sixth space to three fingers' breadths below costal margin. *Liver:* Not enlarged. No tophi.

Case V.—M. S., aged twenty-three years. Daughter of O. A. S. (Case IV). Though always subject to "bilious" attacks with vomiting, she was never jaundiced till eight years ago, when, after typhoid fever, she began to have attacks of pain in the region of the liver, with subsequent passages of gallstones. The stools have been searched for gallstones, and about 200 have been recovered, none larger than a grape-seed. Stools always brown, urine sometimes high colored.

Physical Examination, February, 1910. Rather slightly built, but appears healthy. Skin and conjunctivæ slightly yellow. The *spleen* reaches from the seventh rib to the costal margin, where it is palpable. *Urine:* Bile pigment and urobilin absent. *Blood:* Red cells, 2,084,000; leukocytes, 5800. No nucleated red cells. Slight anisocytosis and poikilocytosis. Differential count normal.

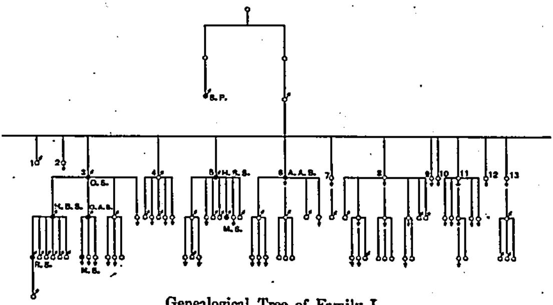
Case VI.—M. S., aged twenty-two years. Son of H. H. S. (Case II). Fifth child. He was born jaundiced, and has remained so ever since. Usually moderate, the yellow color at times becomes very conspicuous, and then he does not feel so well. Since the age of fourteen he has had "bilious" attacks about twice a year, with nausea, vomiting, diarrhœa, anorexia, and fever (up to 101.4°). Duration one or two days. *Never colic. Nosebleed* frequently. The stools have always been dark, the urine high-colored. The bowels move usually twice a day. The patient has been under observation since 1903, during which time there has been little variation in the condition, except that the jaundice has decreased somewhat; the size of the spleen has remained unaltered.

Physical Examination, January 23, 1910. Tall, active, slender youth (six feet two and one-half inches), weighing one hundred and sixty-eight pounds in clothes. Slight jaundice of the skin and conjunctivæ. *Spleen:* From the seventh space to level of navel, 17 cm., hard, rounded. *Liver* not enlarged to percussion, edge just palpable on deep inspiration. Heart not enlarged, systolic murmur in pulmonary area. *Urine:* Bile absent, urobilin sometimes present in traces, sometimes absent, urobilinogen in traces, urochrome abundant. Indican increased. *Feces:* Dark brown, urobilin present. Microscopically normal. *Blood:* Red cells, 4,144,000; leukocytes, 5000 and 9000; differential count normal. No nucleated red cells.

The accompanying family tree chart will serve to render more clear the relationships of the various members of the foregoing family.

Family II. Chronic jaundice in brother, sister, and first cousin once removed.

Case VII.—We owe the chance to study this patient to the kindness of Dr. C. Allen Porter. W. B. W., Mass. General Hospital, No. 162,879. Aged thirty-nine years, married, no children. *Family history:* Mother died of "cirrhosis of the liver, never jaundiced" (probably chronic family jaundice). A first cousin of mother, now forty-one years old, has been icteric since childhood. A sister of the patient, ten years older than he, was jaundiced as far back as he can remember, and had attacks of colic; she died at twenty-one years, of pneumonia. A brother, now fifty years old, has at times yellowness of the eyes, never of the skin. *Past history:* At the age of fourteen the patient noticed a yellow color of his skin, which has persisted ever since, with variations. Attacks of pain in the epigastrium with vomiting began when he was fifteen, and became more frequent and severe as he got older. In 1892 cholecystotomy and removal of 483 gallstones. The spleen was found enlarged at this time. Two later operations to close biliary fistula. Fourth operation in 1905, with removal of many small pigmented calculi. Since then, no further attacks of colic. The patient had bleeding hemorrhoids in boyhood, and *nosebleed* rather frequently, especially five years ago. There has been an ill-defined pain in the right shoulder ever since the last operation. Present illness, March, 1909: Has had a continual ache in the region of the spleen for several months, and feels tired and miserable. Appetite good, bowels inclined to be costive. Has had itching at times, but only of the hands and feet. A fifth operation was performed March 23, 1909, by Dr. C. A. Porter, for the cure of a hernia in the scar of the old wound, and for exploration of the biliary system. The gall-bladder was incised and contained no calculi; no obstruction of the bile ducts could be found.



Genealogical Tree of Family I.

♂ ♀—*Male and female unaffected by the characteristic.*
♂ ♀—*Male and female affected by the characteristic.*
♂——*An individual with a disease which may possibly be associated with the characteristic.*
○——*An individual of unknown sex.*

Physical Examination. Well developed and nourished, considerable pallor. Face a peculiar buff color; the rest of the skin distinctly yellow, conjunctivæ more so. Heart slightly enlarged to left, soft systolic murmur in pulmonary area. Systolic blood pressure, 130. *Liver:* Not enlarged nor palpable. *Spleen:* Much enlarged, hard, smooth, not tender; the long axis very obliquely placed, measures 22 cm. The spleen extends from the seventh rib to the level of the umbilicus, and nearly to the middle line. *Blood:* The serum was reddish yellow and gave a strong reaction for bile. The resistance of the red corpuscles was very kindly tested for us by Dr. F. P. Gay, and a decidedly increased fragility was found. The figures for the hemolysis were as follows: 0.4 per cent. salt solution, 100 per cent.; 0.45 per cent. solution, 60 per cent.; 0.5 per cent. solution, 20 per cent.; 0.6 per cent. solution, 15 per cent.; 0.7 per cent. solution, 10 per cent. Normal blood gives little or no hemolysis with 0.5 per cent. salt solution.[1] There was moderate anemia, with red counts ranging from 4,400,000 to 4,116,000; hemaglobin, 80 per cent. (Sahli); color index, I. White counts, 7200 and 8100. Differential count normal. Polychromatophilia and anisocytosis present. Most of the smears showed a few normoblasts, and once an "intermediate" megaloblast was found.

Urine. The urine was frequently examined, and was always of a high reddish yellow color. Urobilin was constantly present and bile pigment absent. The twenty-four-hour amount normal. Indican increased once, normal at other times. A uric acid deposit was often observed.

Feces. Usually one or two stools a day of a rich orange color, formed, soft, time of passage nineteen hours. Strong reaction for urobilin. During a period when Blaud's pills were being taken, the stools were a deep olive-green color. This disappeared as soon as iron was discontinued, and was probably due to oxidation of bilirubin to biliverdin by the iron. A single stool, when patient was on a purin-free diet, showed a water content of 87 per cent. and normal proportions of neutral fat, fatty acids, and soaps. (Total fat, 29 per cent. of dried stool; of this, there was 38 per cent. neutral fat, 26 per cent. fatty acids, 36 per cent. soaps.)

Stomach Examination. No fasting contents. After Ewald breakfast hypoacidity (free HCl, 0.01 per cent.; total acidity, 0.03 per cent.)

Bile. Some of the bile was obtained aseptically at the operation, and examined. Cultures, both aërobic and anaërobic, made by by Dr. Oscar Richardson, proved sterile. The bile was transparent, and of a deep golden-red color, evidently due to an abundance of bile pigment. Reaction neutral. No macroscopic mucus. Mucin present by acetic acid test. Bilirubin and bile acids present, albumin absent. Sediment negative.

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[1] For the method, see Gay, Jour. Med. Research, 1907, xvii, 321.

Metabolism. In view of the present interest in creatinin, it was thought desirable to determine the amount of this substance. The patient was put on a creatin-free and purin-free diet, and after a preliminary period of three days, the urine was collected. The methods employed were, for the total nitrogen, the Kjeldahl method; for ammonia, urea, creatin, creatinin, the Folin methods; for uric acid, the Folin-Schaffer method. The determinations were made in duplicate. We are greatly obliged to Professor O. Folin for the use of his laboratory and for advice. The figures obtained are shown in the following table:

Date.	Total N. Grams.	NH_3 as N. Grams.	Urea as N. Grams.	Uric acid. Grams.	Creatin. Grams.	Creatinin. Grams.	Creatinin. Milligrams per kilo body weight.
April 16-17	10.81	0.60	8.63	.....	0.066	1.364	21
April 17-18	10.07	0.51	8.12	.....	0.046	1.304	20
April 18-19	9.65	0.61	7.71	.....	0.061	1.208	19
July 8-9	13.13	....	....	0.785	0.000	1.374	20

The values obtained for creatinin and urea are normal, those for ammonia are somewhat high, and the endogenous uric acid is distinctly increased. In the first period the uric acid could not be quantitated because part of the uric acid was precipitated spontaneously.

Family III. Four members affected in three generations.

For the opportunity to study this family we are greatly indebted to Dr. W. H. Smith, of Boston.

CASE VIII.—J. N., aged fifty-five years, of Irish descent, only child. *Family history:* His mother was the color of saffron as long as he can remember, twenty years or more. Her three sisters were all free from jaundice. The patient has had five children; the first was a girl and escaped the disease; the second (Case IX) and third (Case X) are both yellow; the fourth, male, died at the age of seventeen months, unaffected; the fifth, also male, was born jaundiced, and died when five days old. *Personal History:* He has been jaundiced since boyhood. The color is sometimes an intense lemon-yellow, but usually only moderate. It increases after fatigue and "catching cold," but exposure to cold does not affect it. The urine has always been high-colored and the stools brown. Nose bleed during adolescence, never "bilious attacks," or itching. He often has a tired feeling, and a tendency to sleep a great deal, but his general health is better now than when he was younger. Four years ago he had an attack of tremendous pain in the epigastrium lasting several hours (gallstone colic). There were several similar attacks that year, none since.

Physical Examination, March 1910. Small man, height, five feet four inches; weight, one hundred and eight pounds; skin and conjunctivæ of a light yellow color; acne of face. Heart not enlarged, soft systolic murmur in pulmonary area, systolic cardiorespiratory murmur at base, venous hum in neck. Pulse, 76. *Spleen:* Greatly enlarged, reaching from the eighth rib to the level of the anterior superior spine of the ilium, and to the middle line, so that it fills the left half of the abdomen. The surface is hard, smooth, not tender. *Liver:* Not enlarged nor palpable. *Blood:* Red-cells, 3,608,000. Hemoglobin, 70 per cent. (Sahli). Color index, 1. Leukocytes, 6000. Differential count: Polynuclear neutrophiles, 77.25 per cent.; lymphocytes, 19.75 per cent.; mononuclears and transitionals, 2.25 per cent.; eosinophiles, 0.5 per cent.; mast cells, 0.25 per cent. One "intermediate" megaloblast. Anisocytosis present; average diameter (100 cells), 6.48 microns, smallest cell, 4.3, largest, 8.6 microns. No poikilocytosis nor punctate basophilia, slight polychromatophilia. *Urine:* Orange colored, slightest possible trace of albumin, bile absent, urobilin and urobilinogen present. Sediment, no casts or blood. *Feces:* Formed, color a rich golden ochre, acid. Microscopically, numerous starch granules, no excess of fat or muscle fibers; the solid particles are intensely bile-stained. Marked reaction for urobilin, traces of bilirubin.

Case IX.—E. N., aged twenty-three years, son of J. N. At the age of eight he became jaundiced, without other symptoms. As a boy he often felt listless and suffered from nose-bleed. From the age of twelve to fourteen he had pain in the right shoulder, and at fourteen began to have attacks of typical *biliary colic.* Two years later he had 12 gallstones removed at operation; since then there has been no more colic. The jaundice deepens after unusual fatigue, and is more marked in the summer than in the winter. Minor illnesses of any sort cause an increased yellowness. There have been no "*bilious attacks.*" Enlargement of the spleen was first noted in 1907, by Dr. W. H. Smith. The patient does not feel sick at all, and seems alert and active.

Physical Examination, Februray 1910. Rather slightly built, well nourished, skin and conjunctivæ a lemon-yellow color. Heart negative except for a slight systolic murmur in the pulmonary area. Pulse normal in rate. *Spleen:* Considerably enlarged, reaching from the eighth rib to 1 cm. above the navel, long axis 17 cm. *Liver:* Not increased in size. *Blood:* Red cells, 4,032,000. Hemoglobin, 70 per cent. (Dare). Color index, 0.9. Leukocytes, 13,000 at 4 P.M. The fresh blood stained with brilliant cresyl blue shows reticulation in about 10 per cent. of the red corpuscles. In stained smears there is distinct anisocytosis, with decreased average diameter (6.62 microns). No polychromatophilia nor punctate basophilia. No nucleated red cells, blood plates normal. Differential count: polynuclear neutrophiles, 71.25 per cent.; lymphocytes, 21.5 per cent.;

mononuclears and transitionals, 5.75 per cent.; eosinophiles, 1.25 per cent., mast cells, 0.25 per cent. *Urine:* Orange, bile pigment absent, urobilin and urobilinogen in large amounts. Indican not increased. Uric acid and oxalate crystals in the sediment. *Feces:* Formed, color raw Sienna, microscopically normal. Urobilin strongly positive.

CASE X.—F. N., aged twenty years, daughter of J. N. For five years past slight yellowness of the eyes and skin has been noticed. Up to the age of twelve she had frequent *bilious attacks,* with vomiting of bitter stuff, lasting up to three days. Never colic or nose-bleed. The jaundice is increased by late hours and fatigue, and she gave up going to dances for this reason. It becomes more marked in hot weather. For some years she has been pale. Lately her joints are stiff, but limber up with exercise. (Stiffness probably muscular). She often has a feeling of lassitude. Otherwise she is well, except for an abnormal appetite; she does not feel satiated after a hearty meal (bulimia). The bowels usually move twice a day.

Physical Examination. Rather slender girl, but well developed and nourished. The slight tinge of yellow in the skin is rather becoming. The conjunctivæ appear more yellow than the skin. The heart is not enlarged; there is a soft systolic murmur in the pulmonary area. Pulse, 84. *Spleen:* Readily palpable, about 2 cm., below the ribs. *Liver:* Not enlarged. *Blood:* The serum gives a strong reaction for bilirubin. Red cells, 3,564,000. Hemoglobin, 70 per cent. (Sahli). Color index, 1. Leukocytes, 6600. Anisocytosis present, the average diameter of the red cells decreased (6.22 microns). No nucleated red cells. No poikilocytosis, polychromatophilia, or punctate basophilia; platelets normal. Differential count: Polynuclear neutrophiles, 74.75 per cent.; lymphocytes, 20.25 per cent.; mononuclears and transitionals, 3.75 per cent.; eosinophiles, 0.75 per cent.: mast cells, 0.5 per cent. *Urine:* Reddish yellow, no bile or urobilin, urobilinogen present in traces. Indican normal. Slightest possible trace of albumin, but no casts or blood. *Feces:* Soft, greenish yellow, acid. Microscopically there is an excess of neutral fat, with a few calcium soap crystals, but no excess of starch or muscle. Intense reaction for urobilin, considerable bilirubin.

Family IV. At least three members affected in three generations, probably several others. (Investigated through the kindness of Drs. N. A. Ludington and George Blumer, of New Haven).

CASE XI.—J. T., aged fifty-nine and one-half years, male, second child, of Scotch parents. *Family history:* His father, who died at seventy, of pneumonia, suffered from frequent attacks of vomiting of bile, lasting about a day; it is probable that his skin was yellow. Four brothers and one sister lived to grow up; one of the brothers was yellow at times, and probably had the "bilious attacks." A son of this brother is said to be sallow. The patient married his first cousin on the father's side; she is sallow and has pain in the left side of the abdomen. She refused to be examined. Four children resulted from this marriage—two daughters who died in infancy, a son who is jaundiced (Case XII), and another son who is thought to be sallow. The patient's mother had severe arsenical poisoning while pregnant with him. *Past history:* The jaundice probably dates back to early manhood, when he began to have attacks of vomiting of bile, with headache, some pain in the right hypochondrium, and a decidedly yellow color of the skin. These attacks last two or three days, and are associated with an increase of the constipation to which he is subject. He frequently has urticaria, and used to have nose-bleed as a boy. Obstruction of the bowels at the age of twenty-two. Two years later had lead colic (occupation then, rubber-cutter.) For fifteen years he has had attacks of pain in the one or the other great toe, coming on suddenly at night. He has been a hearty eater of meat, and a beer drinker.

Physical Examination. Medium build, well developed, fairly nourished. Skin yellowish; face of a sallow, leathery color; conjunctivæ distinctly yellow. No lead line. The lungs show signs of emphysema. The heart is moderately enlarged to the left, with soft systolic murmurs at the apex and at the aortic area. Aortic second sound rather sharp. Subclavian arteries thickened, radials not. Pulse, 80; systolic pressure, 165 to 170. *Spleen:* Greatly enlarged, measuring 12 by 17 cm., not tender. Liver flatness from fifth rib to costal margin, where the edge of the organ is palpable. Distinct thickening about metatarsophalangeal joints of both great toes. No tophi. *Blood:* Red cells 2,804,000. Hemoglobin, 50 per cent. (Tallqvist). Color index, 0.9. Leukocytes, 7900. Moderate anisocytosis, average diameter normal (7.64 microns). No nucleated red cells. No achromia, poikilocytosis, polychromatophilia, or basophilia. Differential count: Polynuclear neutrophiles, 80.6 per cent., lymphocytes, 15.7 per cent.; mononuclears and transitionals, 2 per cent.; eosinophiles, 1.7 per cent. Urine of normal color; specific gravity, 1009; albumin, a slight trace; no bile or urobilin; a faint trace of urobilinogen present. Indican normal. In the sediment fairly numerous hyaline casts; no blood (chronic interstitial nephritis).

The complication with gout is of interest, but in the presence of lead poisoning and the overconsumption of meat and malt liquors is not surprising.

CASE XII.—G. T., aged thirty-two years, son of J. T. The permanent yellow color was not noticed until ten years ago, but was probably present before that. Since the age of seventeen he has had "*bilious attacks,*" in which he would feel tired, drowsy, and depressed, with jaundice, constipation, and headache, and toward the close of the attack vomiting of bile, or *nose-bleed.* Several such attacks in a year, lasting a day or two. They seem to be brought on by constipation, fatigue, or irregular hours of eating. Light attacks without vomiting once every two weeks. When twenty years old had a severe cramp in the epigastrium, doubling him up, and occasionally since then he has had similar attacks. (*Cholelithiasis.*) He has *hives* frequently, to which an occasional itching of the legs may be attributed. Appetite good, sleeps "unusually well." Stools always dark, "like chocolate." He is said to have had malaria eleven years ago, but had no chills; at that time a doctor found the spleen enlarged. Two months ago a prominent European consultant made a diagnosis of Banti's disease.

Physical Examination. Medium-sized man, sparely nourished. The skin of the body is a pale lemon-yellow, while the face is of a peculiar brownish-yellow, leathery color, unlike the hue of ordinary jaundice. The conjunctivæ are distinctly jaundiced. Heart not enlarged, slight systolic murmur at base. Pulse normal. *Spleen:* Greatly enlarged, measuring 22 x 13 cm., reaching below to the level of the spine of the ilium and to the middle line at the navel. It is smooth and hard, and tender at one point. *Liver:* Palpable at costal margin, area of dulness normal. *Blood:* Serum strongly tinged with bile, and gives a marked Hedenius reaction. Red cells, 3,492,000. Hemoglobin, 65 per cent. (Tallqvist). Color index, 0.9. Leukocytes, 5800. Two normoblasts seen. Marked anisocytosis, average diameter decreased (6.48 microns). No achromia, slight poikilocytosis, some polychromatophilia, no punctuate basophilia, except in one normoblast. Platelets normal. Differential count normal. *Urine:* Orange, contains urobilin and urobilinogen, but no bile. *Feces:* Mushy, yellow (milk diet), alkaline. Numerous shreds resembling connective tissue. Microscopically normal except for increase in the calcium soap crystals. Urobilin strongly positive, bilirubin absent.

Stomach examination after Ewald breakfast: 40 c.c. undigested bread mixed with mucus, free HCl 0, total acidity 5, slight test for lactic acid (chronic gastritis).

CASE XIII.—C. T., aged seven years, son of the foregoing patient, grandson of J. T. The eyes have been yellowish since birth. The color becomes more apparent when he is constipated. He has had no children's diseases, only frequent colds. Nose-bleed once, never colic or vomiting attacks, except after eating strawberries or bananas. Hives frequently. The child has seemed healthy, but never could run like the other boys, and complains of a pain in the left side of the abdomen after exercise. Appetite and digestion good, bowels regular as a rule, sometimes constipated.

Physical Examination: March, 1910. Well developed for his age, and well nourished. He is the least jaundiced of this family, but the skin and conjunctivæ are distinctly though faintly yellow. On the legs, arms, and scrotum a few wheals, one on the scrotum showing hemorrhagic infiltration. Mucous membranes somewhat pale. Heart not enlarged, loud systolic murmur in pulmonary area and venous hum in neck, pulmonic second sound not accentuated.

Spleen: Much enlarged, measuring 18 by 13 cm., smooth, not tender. *Liver:* Slightly enlarged; dulness above at sixth rib; liver palpable 3 cm. below costal margin. *Blood:* The serum on standing shows a green fluorescence and is strongly positive for bile pigment. Red cells, 3,412,000. Hemoglobin, 50 per cent. (Sahli). Color index, 0.74. Leukocytes, 8500. Two normoblasts and one "intermediate" megaloblast seen. Marked anisocytosis, average diameter decreased (6.69 microns). Considerable achromia and poikilocytosis, some polychromatophilia, and very fine punctate basophilia. *Urine:* Somewhat high colored, no bile, urobilinogen absent, urobilin in traces. Indican normal. *Feces:* Formed, dry, yellowish brown, alkaline, microscopically normal. Urobilin present, but reaction with zinc acetate less intense than in the other cases. Bilirubin absent.

An interesting point in this family is the tendency to urticaria, which is present in all three generations.

The bibliography which follows makes no pretence at completeness. Only those articles are included which could be personally verified, hence some foreign references have been omitted. The French literature on the subject is very voluminous, owing to the fact that the same case may be reported twice by different observers, and that some authors feel it necessary to write many articles on the subject. Many such references are purposely omitted.

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